European Annals of Otorhinolaryngology, Head and Neck diseases (2012) **129**, 238—243

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Elsevier Masson France
EM|consulte
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ORIGINAL ARTICLE

Nasal and paranasal esthesioneuroblastomas: Clinical outcomes

J. Michel[a,*], N. Fakhry[a], L. Santini[a], J. Mancini[b], A. Giovanni[a], P. Dessi[a]

[a] *Service d'ORL et chirurgie cervico-faciale, Assistance publique—Hôpitaux de Marseille, CHU La Timone, Aix Marseille université, 264, rue Saint-Pierre, 13385 Marseille cedex, France*
[b] *Service de gestion de l'information médicale, Assistance publique—Hôpitaux de Marseille, CHU La Timone, Aix Marseille université, 264, rue Saint-Pierre, 13385 Marseille cedex, France*

KEYWORDS
Sinus cancer;
Paranasal sinus;
Overall Survival;
Disease-free survival

Summary Esthesioneuroblastomas (ENB) are rare tumours derived from the olfactory epithelium. Based on their experience and a review of the literature, the authors tried to identify the epidemiological, clinical, histological and therapeutic factors that influence overall and disease-free survival in their series of ENB.
Methods: This retrospective study concerned eleven patients treated in a single institution for ENB of the nasal cavity and sinuses between 1978 and 2006. The data collected were submitted to statistical analysis using R 2.0® software. Overall survival and disease-free survival were estimated by the Kaplan-Meier method and prognostic factors were identified by Log-Rank test.
Results: This series comprised three women (27.2%) and eight men (72.8%) (sex ratio: 2.6). The mean age at diagnosis was 56 years (range: 37—69 years). No risk factors were identified in this cohort. The mean follow-up was 110.2 months (range: 7—348 months). This series included three T1 (27.3%), one T2 (9.1%), four T3 (36.3%) and three T4 (27.3%) tumours. The 1-year, 5-year and 10-year disease-free survival rates were 81.8%, 54.5% and 18.2%, and the corresponding overall survival rates were 100%, 90% and 60%, respectively. The main prognostic factors reported in the literature are tumour stage at diagnosis, adjuvant radiotherapy and radiation dose.
Conclusion: ENB are characterized by a high recurrence rate and recurrences can occur a very long time after the diagnosis, indicating the need for prolonged follow-up of these patients. The 5-year and 10-year overall survival rates are about 90% and 60%, respectively.

Introduction

Esthesioneuroblastoma (ENB) was first described in 1924. These rare tumours are derived from olfactory epithelium and usually arise in the olfactory cleft [1,2]. Most published series concern retrospective studies based on small sample sizes. However, several international multicentre studies have been published, based on a greater number of cases, allowing identification of prognostic factors [3]. In a meta-analysis of all published cases from 1924 until 1997, Broich et al. reported a total of 945 cases [2].

* Corresponding author. Tel.: +33 4 91 38 60 71.
E-mail address: justin.michel@ap-hm.fr (J. Michel).

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doi:10.1016/j.anorl.2011.10.007

Table 1 Dulguerov's TNM classification.

Dulguerov's classification [1992]
T1: tumour involving the nasal cavity excluding the sphenoid sinus
T2: tumour involving the nasal cavity including the sphenoid sinus
T3: tumour extending to the orbit or anterior cranial fossa
T4: tumour involving the brain
N0: no cervical lymph node metastases
N1: cervical lymph node metastases
M0: no metastases
M1: distant metastases

Based on our experience and a review of the literature, we tried to identify epidemiological, clinical, histological and therapeutic factors influencing overall survival and disease-free survival in our series of ENB.

Patients and methods

This retrospective study was based on 11 patients managed in our institution for ENB of the nasal cavity and sinuses between 1978 and 2006.

Epidemiological data, clinical and imaging findings, histology, treatment modalities and outcome of patients were studied. To ensure a homogeneous series, Dulguerov's TNM classification, presented in Table 1, was applied to all patients either retrospectively (patients managed before 1992) or prospectively (patients managed after 1992) [4].

The database was created with FileMaker Pro® software (version 5; Microsoft Corp. Ltd, Redmond, USA). Statistical analysis of overall survival and disease-free survival was performed according to the Kaplan-Meier method. The prognostic value of the following elements on overall survival and disease-free survival was investigated by univariate analysis (Log-Rank test): age, gender, T status, tumour extension (involvement of key structures such as the sphenoid sinus, frontal sinus, orbit, eyeball, anterior cranial fossa, cavernous sinus, brain), histological grade, surgical management and adjuvant radiotherapy. For all tests, a P value less than 0.05 was considered statistically significant. All statistical analyses were performed with R 2.0® software.

Results

Epidemiological data

This series comprised three women (27.2%) and eight men (72.8%), i.e. a sex ratio of 2.6. The mean age at diagnosis was 56 years (range: 37—69 years). The tumour was located on the right side in four cases (36.4%), the left side in three cases (27.2%) and the lesion was bilateral in four cases (36.4%). No occupational exposure risk factor (leather tannin, wood dust, exposure to nickel) was identified. The median follow-up was 102 months (range: 7—348 months).

Clinical features

Initial symptoms were unilateral in 90.9% of cases. The most common symptoms were nasal obstruction (70%) and epistaxis (30%). Other presenting complaints were pain (20%), diplopia or exophthalmos (20%), neurological signs (20%) and skin signs (10%).

Site, extension and TNM classification

The initial assessment in all patients managed after 1991 ($n = 10$) comprised contrast-enhanced CT scan of the facial bones for local staging and contrast-enhanced CT of the neck and chest for regional and distant staging. This assessment was completed by MRI of the facial bones in eight patients (80%). Review of imaging allowed assessment of tumour sites, modes of extension and staging. The initial assessment for the patient diagnosed in 1976 was not available for review.

In every case, the tumours arose from the olfactory cleft. The lesion was strictly confined to one nasal cavity in two cases (18.2%), and extended to the sphenoid sinus in one case (9.1%), the frontal sinus in one case (9.1%), the orbit in two cases (18.2%), the eyeball in one case (9.1%), the anterior cranial fossa in three cases (27.3%), the cavernous sinus in one case (9.1%) and the brain in three cases (27.3%).

This series comprised three stage T1 (27.3%), one stage T2 (9.1%), four stage T3 (36.3%) and three stage T4 (27.3%) tumours. One patient (9.1%) had positive lymph nodes at diagnosis and was staged as T4N2c (retropharyngeal, spinal and bilateral jugulo-carotid lymphadenopathy). No patients had metastatic disease at diagnosis.

The patient with a high-grade malignant tumour with lymph node invasion at the initial diagnosis was alive with disease at the time of data collection, i.e. 68 months after the diagnosis.

Histological data

The histological grade was determined for only eight (63.6%) of the 11 cases of histologically documented ENB: grade I in one case (12.5%), grade II in two cases (25%), grade III in three cases (37.5%) and grade IV in two cases (25%). The immunohistochemical profile of the tumour was determined in six6 cases. At least one neuroendocrine marker was present in all cases (Neuron-Specific Enolase [NSE], Chromogranin or synaptophysin). PS 100 was positive in four cases and negative in two cases. Epithelial markers were negative in five cases and positive in one case.

Treatment modalities

The initial treatment consisted of four different modalities: surgery alone: 27.3% ($n = 3$); surgery followed by adjuvant radiotherapy: 36.3% ($n = 4$); concurrent chemoradiotherapy (cisplatin/5-fluorouracil): 18.2% ($n = 2$); neoadjuvant chemotherapy (cisplatin/etoposide and cisplatin/5-fluorouracil) (18.2%) followed by chemoradiotherapy in one case and surgery in one case, both staged as T4N0M0.

Table 2 Esthesioneuroblastoma — local recurrence, regional recurrence and distant recurrence as a function of TNM status and initial treatment modalities.

T status	Initial treatment	Total number of patients	Local recurrence	Regional recurrence	Distant recurrence
T1	Surgery + RT	1	1	0	0
	Surgery alone	2	1	0	1
T2	Surgery + RT	1	0	0	0
T3	Surgery + RT	1	0	0	0
	CRT	1	0	0	0
T4	Surgery alone	1	1	0	0
	Surgery + RT	1	0	1	0
	CT + Surgery	1	1	0	0
	CT + CRT	1	0	1[a]	0
	CRT	1	1[a]	0	0

Surgery + RT: surgery followed by radiotherapy; Surgery alone: surgery alone; CRT: concurrent chemoradiotherapy; CT + Surgery: chemotherapy followed by surgery; CT + CRT: chemotherapy followed by concurrent chemoradiotherapy.
[a] Patients with progressive disease on completion of initial treatment.

Overall, eight patients (72.2%) were operated, five via a craniofacial incision (one T1, three T3 and one T4), two by degloving (one T1 and one T2) and one by endonasal surgery (T1). Macroscopically negative surgical margins were obtained in all operated patients. Surgical margins were negative on histological examination in seven of these eight cases. The pathologist was unable to provide this information for one case due to fragmentation of the operative specimen.

Radiotherapy was delivered according to a nonfractionated protocol at doses ranging between 45 and 70 Gy to the tumour bed. The patient with T4N2c disease received a dose of 56 Gy to the tumour bed and lymph node areas.

Actuarial 1-year, 5-year and 10-year disease-free survival rates were 81.8%, 54.5% and 18.2% and actuarial 1-year, 5-year and 10-year overall survival rates were 100%, 90% and 60%, respectively.

Eight treatment failures (72.7%) were observed. Two patients, one T4N0 and one T4N2c, (18.2% of all patients) presented progressive disease on completion of initial treatment and another six patients relapsed and were staged as T1 in three cases and T4 in three cases. Results for local and distant recurrence are presented in Table 2, according to site, TNM, and treatment modalities. The mean recurrence-free survival was 53 months (range: 16—115 months).

Patients who developed recurrence were treated by redo surgery in three cases, chemoradiotherapy (cisplatin/5-fluorouracil) in one case, chemotherapy alone in one case and radiotherapy alone in one case. Salvage therapy for late recurrence (9 and 11 years) was effective in two cases. These two patients were in complete remission at the time of data collection (with a follow-up of 2 years and 21 years, respectively). Treatment of local recurrence was surgical in both cases.

Three patients died from progression of their disease (one T1 and two T4) and three patients were alive with disease at the time of data collection.

Univariate analyses failed to demonstrate any prognostic impact on overall survival and disease-free survival for any of the variables tested, especially tumour extension (Table 3).

Discussion

This study shows that ENB are rare tumours that can be associated with very long survival. The age, sex ratio and lateralisation of the tumours in this series are identical to those reported in the literature [5—7]. No male or female predominance has been reported [1,8]. These tumours usually present during the sixth and seventh decades, but cases

Table 3 Results of univariate analyses of the prognostic impact of the variables studied in our series on overall survival and disease-free survival.

Variable tested	Impact on overall survival	Impact on disease-free survival
Age	Not significant ($P = 0.874$)	Not significant ($P = 0.31$)
Gender	Not significant ($P = 0.403$)	Not significant ($P = 0.754$)
Dulguerov T status T1 vs T2 vs T3 vs T4	Not significant ($P = 0.786$)	Not significant ($P = 0.255$)
Dulguerov T status T1T2 vs T3T4	Not significant ($P = 0.874$)	Not significant ($P = 0.369$)
Tumour extension (sphenoid, frontal sinus, orbit, eyeball, anterior cranial fossa, cavernous sinus, brain)	Not significant ($P = 0.874$)	Not significant ($P = 0.369$)
Histological grade	Not significant ($P = 0.754$)	Not significant ($P = 0.31$)
Surgery vs other treatment modalities	Not significant ($P = 0.874$)	Not significant ($P = 0.525$)
Adjuvant radiotherapy versus surgery alone	Not significant ($P = 0.256$)	Not significant ($P = 0.31$)

Table 4 Five-year and 10-year disease-free survival (DFS) and overall survival (OS) of esthesioneuroblastoma indicating the percentage of patients treated by surgery and adjuvant radiotherapy.

Authors	Patients(*n*)	5-year DFS (%)	10-year DFS (%)	5-year OS(%)	10-year OS (%)	Adjuvant RT rate (%)
Beitler et al. [6]	14	57	41	86	70	100
Dulguerov et al. [8]	390	41	52	45	—	—
Diaz et al. [5]	30	69	38	89	81	77
Jethanamest et al. [1]	311	—	—	62.1	45.6	—
Bachar et al. [7]	39	76	44.7	87.2	69.2	76
This series	11	54.5	18.2	90	60	44

have also been reported in children and in elderly subjects over the age of 80 years [1,2]. The absence of prognostic significance of these factors on survival, as observed in this study and as reported in the literature, is probably due to the very small sample sizes of published series. Similarly, no risk factor for the pathogenesis of these tumours has ever been identified [8].

The initial clinical symptoms of tumours of the facial bones, including ENB, are often nonspecific [9]. The symptoms most commonly reported in the literature are identical to those described in our study [2,8].

The main prognostic factor for overall survival and disease-free survival reported in the literature is clinical stage at the time of diagnosis [1,4,7]. ENB staging can be evaluated according to two classifications: the Kadish classification modified by Morita and the Dulguerov TNM classification [4,10]. Based on a cohort of 311 patients, Jethanamest et al. showed that 10-year overall survival and disease-free survival (Kaplan-Meier analysis) were 83.4% and 90%, respectively, for patients with a tumour confined to the nasal cavity (modified Kadish Type A), 49% and 68.3% for patients with a tumour involving the paranasal sinuses (modified Kadish Type B), 36% and 66.7% for patients with a tumour extending beyond the paranasal sinuses (modified Kadish Type C) and 13.3% and 35.6% for patients with metastatic disease (modified Kadish Type D) ($P < 0.01$) [1,11]. These results are similar to those reported in the meta-analysis by Broich et al. [2] and similar results have also been published for T status of Dulguerov's TNM classification. In a series of 39 patients, Bachar et al. demonstrated a statistically significant survival difference according to T stage with 5-year and 10-year overall survivals of 100% for T1, 100% and 89% for T2, 89% and 53% for T3 and 56% and 28% for T4. Disease-free survival was also significantly influenced by Dulguerov's T status in Bachar's series [7]. Like Bachar et al., we also used Dulguerov's classification, which appears to be the most appropriate classification [7], as it reliably reflects the course of these tumours by allowing a good description of local tumour extension.

The results of the present series are compared to those of the literature in Table 4 [1,5—8]. All studies confirm the possibility of late recurrence many years after the initial diagnosis [4,5].

The positive lymph node rate at the time of diagnosis varies according to the studies between 5 and 10% [1,12], with a similar rate in the present series. Jugular lymph nodes are most commonly involved, but retropharyngeal lymph node involvement, as observed in the patient with T4N2c disease, is not exceptional in ENB [13]. In 2008, Zollinger et al. reported four cases of metastatic disease in this territory in a series of 17 patients managed for ENB [14]. Patients with lymph node metastases at the time of diagnosis require multimodal management, comprising surgery and radiotherapy, as soon as possible [13]. There are no arguments in the literature in favour of the use of surgery alone or radiotherapy alone [13]. No consensus has been reached concerning the optimal management of patients with clinical and radiological N0 disease. However, as the frequency of recurrence at this site ranges from 15 to 30% in the literature [8,12,15], most authors agree that prophylactic treatment of cervical lymph nodes must be considered in the presence of a locally advanced tumour. [8,12,15]. The development of late metachronous lymph node metastases (more than 6 months after the initial diagnosis) is not rare. Gore et al., in a meta-analysis based on 678 patients, reported late metachronous lymph node metastases in 12.8% of cases [16]. These lymph node metastases also require multimodal treatment at least including surgery, whenever possible, and radiotherapy [13,16]. The presence of lymph node metastases has been reported to be a factor of poor prognosis [8,17]. Distant metastases are rare and are also associated with a very poor prognosis [8].

Well-differentiated ENB is a simple diagnosis. Immunohistochemistry is a very valuable tool in less well-differentiated forms. Three differential diagnoses must be considered: neuroendocrine carcinoma, mucosal melanoma and sinonasal undifferentiated carcinoma (SNUC) [18,19].

Discordant results have been published concerning the prognostic value of histological grade [19]. In several studies, Hyams' classification appeared to have a significant prognostic value: 56% survival in grade I-II (low-grade) and 25% survival in grade III-IV (high-grade) [2,8,20], but this association was not confirmed in the present series.

Several studies have compared the respective results of surgery alone, radiotherapy alone, the combination of surgery and radiotherapy and the contribution of chemotherapy [1,5,21]. Surgery followed by adjuvant radiotherapy appears to be superior to radiotherapy or surgery alone [5]. Based on a series of 274 patients, Jethanamest et al. confirmed that the mean survival of patients treated by a combination of surgery and radiotherapy was 216.8 months (range: 188—245) versus 208 months for surgery

alone and 92.8 months for radiotherapy alone ($P < 0.002$ radiotherapy versus combined therapy) [1]. Similar results were published by Foote et al. in 1993 [11]. Although these survival differences were not observed in the present series, probably because of the small sample size, management of these tumours in our centre now systematically comprises adjuvant radiotherapy. The multicentre study conducted by Ozsahin et al. in 77 patients demonstrated the prognostic value of negative surgical margins [3].

Several authors have reported the possibility of complete endoscopic resection of tumours confined to the nasal cavity and paranasal sinuses. A neurosurgical approach, possibly combined with a transfacial approach, is recommended by most authors for the treatment of lesions extending to the skull base [22—25]. The place of endoscopic surgery in the treatment of ENB was the subject of a meta-analysis based on 361 patients operated between 1992 (date of the first known publications on endoscopic surgery) and 2008 [26]. The authors found better survival rates (overall and disease-free survival) after endoscopic surgery than after open surgery. However, these results are influenced by the fact that open surgery is mainly performed for Kadish stage C and D disease. The authors concluded that endoscopic surgery is possible but must be reserved to less advanced tumours [26]. The number of studies comparing these two types of surgery for advanced tumours is insufficient at the present time [26].

Radiation doses have also been reported to be a prognostic factor in some studies. Ozsahin et al. showed that a minimum dose of 54 Gy to the tumour bed provides a good chance of survival [3]. We did not demonstrate any impact of adjuvant radiotherapy on the survival of our patients, probably because of the small sample size.

The value of chemotherapy has been poorly evaluated on the basis of small series [27]. Chemotherapy can be proposed either in the adjuvant setting for curable lesions in combination with radiotherapy, or for unresectable advanced or metastatic tumours. The molecules most commonly used are cisplatin and etoposide or doxorubicin or vincristine [28]. Neoadjuvant chemotherapy (induction chemotherapy) for advanced tumours, using cisplatin and 5-fluorouracil or etoposide, doxorubicin or vincristine, has also been reported in the literature [28]. Most teams using chemotherapy also delivered sequential or concurrent radiotherapy [28]. Encouraging results have been obtained, indicating that the treatment of ENB must be multimodal. Hyams' classification appears to be predictive of the response to chemotherapy [27]. Only patients with very advanced disease were treated by chemotherapy in the present series.

Only two of the six patients with local or regional failure responded to salvage therapy. Salvage therapy appears to be of limited efficacy and every effort must be made to achieve local control during initial treatment.

No consensus has been reached concerning the practical modalities of follow-up of ENB. However, all authors agree on the importance of prolonged follow-up in these patients, as recurrences can occur more than 10 years after the initial diagnosis [29]. In our series of eight patients in treatment failure, 50% relapsed after 5 years and two of them relapsed after 10 years. Follow-up must be based on clinical, endoscopic and radiological examination [29]. MRI is the preferred examination to distinguish recurrence from post-treatment tissue changes [29].

Conclusion

ENB is characterized by the frequency of recurrences, which can occur many years after the diagnosis, justifying prolonged follow-up of these patients. Five-year and 10-year overall survival rates are about 90% and 60%, respectively.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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